PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IN2005/000019	17.01.2005	19.01.2004

International Patent Classification (IPC) or both national classification and IPC
C07D209/52

Applicant
LUPIN LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Deutsch, W Telephone No. +49 89 2399-8281

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IN2005/000019

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☒ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3,4-15
	No:	Claims	1,2
Inventive step (IS)	Yes:	Claims	5-13,15
	No:	Claims	1-4,14
Industrial applicability (IA)	Yes:	Claims	1-4
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

III

According to rule 13.1 PC, an international application shall relate to one invention or to a group of inventions so linked as to form a single inventive concept.

The problem to be solved by invention 1 is considered to relate to the provision of alternative processes for the preparation of the optically pure Ramipril(I), which is a known compound (cf e.g. US6407262B1)

The problem to be solved by invention 2 is considered to relate to the provision of a process for the preparation of anhydrous Ramiprill (I)

The solution to the above problems is completely distinct.
The solution to invention 1 involves the crystallisation of optically impure Ramipril (I) from an organic solvent, whilst the second involves the heating of Ramipril(I) monohydrate
The above solutions are considered to be distinct and not to have a common inventive concept, since no special feature can be identified, which defines a contribution over the prior art. There is also an a posteriori lack of unity between
the two invention in view of the fact that the first invention is known from US6407262B1

V and VI

Reference is made to the following documents:

D1: US-B1-6 407 262 (WANG ZHI-XIAN ET AL) 18 June 2002 (2002-06-18)
D2: US-A-4 587 258 (GOLD ET AL) 6 May 1986 (1986-05-06)
D3: US-B1-6 541 635 (TIEN MONG-JONG ET AL) 1 April 2003 (2003-04-01)
D4: WO 2004/064809 A (SANDOZ GMBH; BHARATRAJAN, RAMASWAMI; ZEISL, ERICH; KOFLER, NIKLAUS; PA) 5 August 2004 (2004-08-05)
D5: US-A-5 061 722 (TEETZ ET AL) 29 October 1991 (1991-10-29)

Invention 1

Novelty

Claims 1 and 2 are anticipated by claims 1-8 and 20-36 as well as the examples of D1. For the claim 2 (cf the case that organic solvent in D1 is an aliphatic ester).

Inventive Step

The closest prior art is considered to be D1, in view of the fact that this discloses a process for the preparation of Ramipril(I), using organic solvents to obtain the desired optical isomer.

In view of the disclosures of D1, it is considered that the skilled person would have arrived at the claims 1-4.

The problem underlying the invention is therefore considered to be the provision of a further crystallisation process for obtaining optically pure Ramipril(I) having surprising effects compared to the processes of D1.

In the absence of any evidence for a surprising effect compared with the prior art an inventive step cannot be acknowledged.

Invention 2

Novelty

None of the documents D1-D3 or D5 disclose hydrated forms of Ramipril (I), such that claims 5-15 are novel

Inventive Step

Claims 5-13, 15

The closest prior art is considered to be D1-D3 or D5.

These documents disclose Ramipril (I), but not the hydrated form.

The problem underlying claims 5-13 and 15 is considered to be the provision of a further form of Ramipril (I) having a surprising effect compared to the closest prior art forms.

On page 9 of the description a comparison is made between the physical characteristics of the monohydrate (e.g. bulk density) of the invention compared to samples from D5.

These improved effects are considered to demonstrate an inventive step for claims 5-13 and 15.

Claim 14

It may be noted here that although not explicitly described as being anhydrous, Ramipril (I) according to D1-D3 and D5 are regarded as being anhydrous, since no solvate or hydrate is indicated.

Thus there appears to be a reconversion of an anhydrous form via a monohydrate back into an anhydrous form.

In this case it is unclear what problem it is intended to solve or what advantage such a process would have over the prior art.

The Applicant has made available a new intermediate (the monohydrate), which can be reconverted back into anhydrous form. This is not considered to be obvious, such that an inventive.

Certain Cited Documents

For the purposes of this communication it has been assumed that the priority of the present application is valid.

In this case D4 does not constitute prior art within the meaning of Rule 64.1 (b).

The claims however are not anticipated by D4 and does not effect the conclusions reached in this written opinion.

VII

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D2 and D3 are not mentioned in the description, nor are these documents identified therein.

VIII

The claims should as far as possible not rely on the description for their meaning, therefore the chemical formula. Having regard for Ramipril(I) in the claims, the chemical formula is given in the description

Claim 5 defines the crystal form through the presence of peaks, without however clearly indicating the relative intensities of these peaks. This is considered to be insufficient for clearly characterising the crystal form.